

Appl. No. 10/791,166
Amdt. dated March 17, 2006
Reply to Office Action of November 18, 2005

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REMARKS/ARGUMENTS

Upon entry of this amendment, claims 1, 4, 7, 10 and 13 are pending in the application. Claims 2-3, 5-6, 8, 9, 11-12 and 14-18 have been canceled without prejudice to subsequent revival. Claim 1 has been amended. Entry of the amendment, reconsideration of the rejection, and allowance of claims 1, 4, 7, 10 and 13 are respectfully requested.

The Amendment

In order to expedite prosecution of the application and advance the case toward allowance, the claims have been amended. No new matter was added by the amendment.

Claim 1 has been amended to specify that the condition is selected from the group consisting of rheumatoid arthritis, alveolitis and atherosclerosis. Support for this amendment can be found in the specification, for example, in paragraph 0006. Therein, the Applicants disclose that MCP-1 has been implicated as an important factor in mediating monocytic infiltration of tissues in inflammatory processes such as rheumatoid arthritis and alveolitis as well as atherosclerosis. See, *e.g.*, Koch, *J. Clin. Invest.* 90:772-79(1992) and Jones, *J. Immunol.* 149:2147-54 (1992) (incorporated by reference in the specification in paragraph 0006; copies are enclosed for the Examiner's convenience). Additional support can be found, for example, in paragraph 0008 and in Boring *et al.* (1998) *Nature* 394:894-897 (a copy is enclosed for the Examiner's convenience).

Claims 1 and 10 have been amended to specify that the antagonist is presented in a pharmaceutical *composition* (as in canceled claims 3 and 12) rather than a pharmaceutical *carrier*. This provides correct antecedent basis for dependent claims 4 and 13. Support for this amendment can be found on page 9, paragraph 0018.

Priority

The Office Action notes that Application No. 08/182,962 which was filed on January 13, 1994, provides support for administration of MCP-1 receptor antagonists for treatment of disease, but MCP-1 receptor antagonists are allegedly not the same as antibodies. The Examiner alleges that according to the '962 specification (and all other applications from

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which the instant application claims priority), antagonist are structurally undefined and are to be identified by performing screening assays. The Office Action concludes that the filing date for the claims drawn to methods of treating disease by administering antibodies receive the benefit of March 1, 2004. The Applicants are urged to point out the specific page and line numbers of the previously filed applications that provide support for the concept of administering antibodies for the treatment of disease if the Applicants disagree with the Examiner's determination of priority.

It is stated for the record that claim 1 (drawn to a method for inhibiting a condition characterized by monocytic infiltrates via administering an MCP-1 receptor antagonist such as an antibody which binds to an MCP-1 receptor polypeptide) should be assigned the priority date of January 13, 1995 in accordance with the parent application 08/446,669, now U.S. Patent No. 6,132,987 (herein the '987 patent). The '987 patent incorporates by reference U.S. Patent No. 5,194,375 which teaches the use of monoclonal antibodies as antagonists for receptor proteins (see column 16, line 59 of the '987 specification). This is evidenced by the instant specification, particularly paragraphs 0084 and 0085. The instant specification teaches the following in paragraphs 0084 and 0085:

[0084] The antagonist is identified by adding an effective amount of an organic compound to the culture medium used to propagate the cells expressing the N-terminal domain of MCP-1 receptor. An effective amount is a concentration sufficient to block the binding of MCP-1 to the receptor domain. The loss in binding of MCP-1 to the receptor may be assayed using various techniques, using intact cells or in solid-phase assays.

[0085] For example, binding assays similar to those described for IL-7 in U.S. Pat. No. 5,194,375 may be used. This type of assay would involve labelling MCP-1 and quantifying the amount of label bound by MCP-1 receptors in the presence and absence of the compound being tested. The label used may, for example, be a radiolabel, e.g., ¹²⁵I or a fluorogenic label.

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U.S. Patent No. 5,194,375 which is incorporated by reference in paragraph 0085 states the following in column 19, Example 6, lines 56-66 of its specification:

Preparation of Monoclonal Antibodies to IL-7R

Preparations of purified recombinant IL-7R, for example, human IL-7R, or transfected COS cells expressing high levels of IL-7R are employed to generate monoclonal antibodies against IL-7R using conventional techniques, for example, those disclosed in U.S. Pat. No. 4,411,993. Such antibodies are likely to be useful in interfering with IL-7 binding to IL-7 receptors, for example, in ameliorating toxic or other undesired effects of IL-7, or as components of diagnostic or research assays for IL-7 or soluble IL-7 receptor.

The specification further states in paragraph 18 on page 6:

[0018] A further aspect of the invention therefore are pharmaceutical compositions containing a therapeutically effective amount of an MCP-1 antagonist identified using the assays of this invention. Such MCP-1 antagonist compositions may be employed in therapies for atherosclerosis, cancer and other diseases characterized by monocytic infiltrates. An additional aspect therefore, the invention includes a method for treating these and/or other diseases and pathological states by administering to a patient a therapeutically effective amount of MCP-1 antagonist, or an active fragment thereof, in a suitable pharmaceutical carrier. [Emphasis added.]

Thus, it is clear from the specification (and parent specifications) that the Applicants have contemplated the use of antibodies to the MCP-1 receptor for the treatment of diseases that are characterized by monocytic infiltration in 1995. One of skill in the art would understand that the use of antibodies (including monoclonal antibodies) as antagonists to MCP-1 receptor could be easily accomplished by following the teachings of U.S. Patent No. 5,194,375 and the conventional techniques of U.S. Pat. No. 4,411,993. Just as antibodies are useful in

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interfering with IL-7 binding to IL-7 receptors, the same is true for antibodies to MCP-1 receptor. Such antibodies would interfere with MCP-1 ligand binding to MCP-1 receptors, thereby acting as antagonists. Thus, the Applicants must not re-teach how to use antibodies as antagonists to a receptor protein if others have already taught so in the prior art. Such antagonists can be used to inhibit monocytic infiltration as taught by the specification.

Rejections Under 35 U.S.C. §112

Claims 1, 4, 7, 9-10, 13, 16 and 18 are rejected under 35 U.S.C. §112, first paragraph, as being allegedly not enabled. The Examiner states that the specification is enabling for a method of administration of anti-MCP-1 receptor antibodies but is allegedly not enabling for inhibition of any condition characterized by monocytic infiltrates. Thus, the Examiner maintained the rejection.

The rejection is respectfully traversed to the extent that it applies to the claims as amended.

In order to advance the case towards allowance, the claims have been further amended. Claim 1 has been amended to specify that the condition characterized by monocytic infiltrates is rheumatoid arthritis, alveolitis or atherosclerosis. Claims 16 and 18 has been canceled.

With respect to the conditions characterized by monocytic infiltrates, the Applicants disclose that MCP-1 has been implicated as an important factor in mediating monocytic infiltration of tissues in inflammatory processes such as rheumatoid arthritis and alveolitis. See, *e.g.*, Koch *et al.*, *J. Clin. Invest.* 90:772-79(1992) and Jones *et al.*, *J. Immunol.* 149:2147-54 (1992). See paragraph 0006 of the specification. Koch *et al.* showed that patients who suffer from rheumatoid arthritis have significantly elevated levels of serum MCP-1 compared to normal serum MCP-1 levels and that MCP-1 itself may function to activate newly recruited mononuclear phagocytes, thereby perpetuating the inflammatory response in the synovial tissue (*e.g.*, MCP-1 has been shown to activate monocytes) (see page 778, Koch *et al.*, 1st column, last paragraph, and 2nd column, first paragraph). Jones *et al.* studied the functional role of MCP-1 in rat models of human disease and showed that MCP-1 plays an important role in

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the pathogenesis of IgA immune complex alvelolitis (*i.e.*, IgA immune complex-induced lung injury) in rats. Lung injury is mediated by infiltration of monocytes and macrophages (see page 2148, Jones *et al.*, 1st column, 1st and 2nd paragraphs).

Further, the Applicants have continued their work as evidenced by Boring *et al.* (1998) *Nature* 394:894-897 (a copy is enclosed for the Examiner's convenience). In Boring *et al.*, the Applicants have shown that MCP-1 is linked to the development of atherosclerosis (see abstract). The Applicants generated mice that lack the MCP-1 receptor and crossed them with mice that lack apolipoprotein E (which develop severe atherosclerosis). The Applicants then showed that the selective absence of the MCP-1 receptor decreases the lesion formation quite markedly in apolipoprotein E lacking mice (see abstract). Thus, the Applicants were able to determine that the MCP-1 receptor is a genetic determinant of atherosclerosis *in vivo* and they provided strong evidence for a direct non-cholesterol mediated effect of MCP-1 in macrophage recruitment and atherogenesis (see page 896, second column, second paragraph).

Thus, it is clear from these publications and the teachings of the specification that the blocking of MCP-1 to its MCP-1 receptor interferes with monocytic infiltration which is implicated in a variety of diseases. The courts have repeatedly held that a "patent need not teach, and preferably omits, what is well known in the art" (*Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Company et al.*, 221 USPQ 481 (Fed. Cir. 1984)).

Further, the Examiner has conceded the following points:

- the amount of experimentation required to make an antibody which binds to SEQ ID NOS: 2 and 4 and inhibits the activity of the receptor is not undue
- there is sufficient guidance to which antibodies can be used in light of the amendments to claim 1
- paragraph 0028 provides support for adequate enablement of conditions characterized by monocytic infiltrates

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However, the Office Action indicates that the Applicants have argued that there is adequate support for the limitation "therapeutically effective amount", which appears in claim 10. Herein, the Office Action indicates that the specification does not provide adequate guidance for the skilled artisan to be able to administer a therapeutically effective amount, despite the disclosed range of about 10 ug to about 1 mg per ml per dose administered. Specifically, the Examiner states that this range is very broad and since the units are recited in "per milliliter per dose administered" and there is allegedly no guidance as to how many ml are to be administered, it is only guidance to the concentration but not to the dose, and trial-and-error experimentation would be allegedly required by the skilled artisan.

As indicated in the Applicant's last response, the specification provides a clear definition of *an effective amount* in paragraph 0084, *i.e.*, a concentration sufficient to block the binding of MCP-1 to the receptor domain. This can be measured, for example, by calcium flux (see page 38, paragraph 0130 of the specification; MCP-1 induced a rapid rise in intracellular calcium in 293 cells that were stably transfected with MCP-1RB). The Applicants teach on page 40 (see paragraph 0135) that the hallmark function of MCP-1 is the induction of chemotaxis (*i.e.*, the migration of cells along a concentration gradient) and that modest increases in intracellular calcium are sufficient to initiate and support monocyte chemotaxis. In addition, the skilled artisan is fully aware that the effective amount of an antibody is the concentration sufficient to block the binding of the ligand to its receptor, thereby preventing receptor activation. Since the Examiner has conceded that it does not require undue experimentation to make an antibody which binds to SEQ ID NOS: 2 and 4 in order to inhibit the activity of the receptor, this rejection should be withdrawn.

The Applicants have previously indicated that the use of an antibody is considered a *routine procedure* which was acknowledged by the Examiner (please see the Applicants' last response filed on September 27, 2005, page 11). The effective amount of an antibody that binds to a receptor protein in order to inhibit the activation thereof is part of the standard practice in the art of molecular biology. In addition, the effective amount of the antibody is taught to be about 10 µg/ml to about 1 mg/ml. The Office Action indicates that this range is very broad and that there is allegedly no guidance as to how many milliliters are to be administered. However, such

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determination is routine and not undue. The Examiner is reminded that some experimentation is permissible.

"The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" (*In re Certain Limited -- Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A. B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985)).

In light of the amendments and arguments presented above, the rejection of claims 1, 4, 7, 9-10 and 13 under 35 U.S.C. §112, first paragraph, should be withdrawn.

Claims 1, 4, 7, 9-10, 13, 16 and 18 are rejected under 35 U.S.C. §112, first paragraph for allegedly lacking written description. The Examiner concedes that the term "about 10 µg/ml to about 1 mg/ml" appears in the instant specification and the parent specifications. However, according to the Office Action, the recitation of this term is drawn to the effective amount of uncharacterized antagonist which is to be identified via a screening assay, and the recitation of this term does allegedly not constitute adequate support for administration of antibodies at this concentration.

The rejection is respectfully traversed.

Applicants point the Examiner to paragraphs 0084 and 0085 of the specification, wherein the Applicants discuss how to identify antagonists, including antibodies. As indicated above, the Examiner has conceded that there is *sufficient guidance to which antibodies* can be used in the claimed methods. The effective amount of an antibody that binds to a receptor protein in order to inhibit the activation thereof is a standard practice in the art.

Moreover, MPEP 2163 indicates that the description need only describe in detail that which is new or not conventional (see *Hybritech v. Monoclonal Antibodies*, 802 F.2d at 1384, 231 USPQ at 94). In addition, the courts have held that "disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides adequate written description of an antibody claimed by its binding affinity to that antigen." (see *Noelle v. Lederman*, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir.

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2004). Since the structure of the MCP-1 receptor is known and making and using an antibody to a receptor protein is standard in the art, the written description requirement is met and the rejection should be withdrawn.

The Office Action further states that all recitations of administration of monoclonal antibodies are considered new matter because they were allegedly not contemplated in the parent specifications. The Applicants have addressed this issue in detail in the priority section wherein it is shown that antibodies were contemplated in 1995 (please see above).

Claim 18 is rejected under 35 U.S.C. §112, second paragraph for allegedly being indefinite. Claim 18 has been canceled. Thus, this rejection is moot.

Rejection under 35 U.S.C. §102(b)

Claims 1, 7, 9, 10, 13, 16 and 18 are rejected under 35 U.S.C. §102(b), for allegedly being anticipated by LaRosa *et al.*, U.S. Patent No. 6,312,689.

This rejection is respectfully traversed.

Since La Rosa *et al.* was issued on November 6, 2001 and the instant application has a priority date of January 11, 1995, La Rosa *et al.* does not qualify as a reference under 35 U.S.C. §102(b). The issue of priority has been addressed in detail in the priority section above. Claims 16 and 18 have been canceled.

Rejection under 35 U.S.C. §103(a)

Claims 4 and 13 are rejected under 35 U.S.C. §103(a), for allegedly being obvious over LaRosa *et al.*, U.S. Patent No. 6,312,689.

The rejection is respectfully traversed.

As indicated above, La Rosa *et al.* was issued on November 6, 2001 and the instant application has a priority date of January 11, 1995. Thus, La Rosa *et al.* does not qualify as a reference under 35 U.S.C. §103(a) either.

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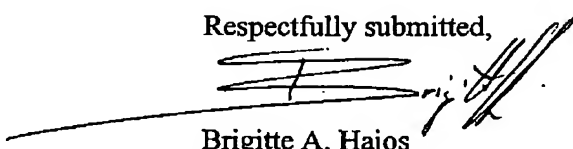
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CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Attachments: Publications by Jones *et al.* and Koch *et al.* and Boring *et al.*
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